REMARKS

The Official Action dated January 29, 2008 has been carefully considered. By present amendment, claim 1 is amended to detail "exposure" with support found, e.g. at page 7, lines 4, 10 and 12. Claims 10, 13, 17, 18 are amended merely for clarification and consistency of language. Claim 22 is amended in accordance with teachings found at page 4, lines 15-22. Claim 24 is amended to specify an embodiment direct to a human infant, as disclosed on page 5, lines 22-23, and to clarify details relating to this embodiment as disclosed on page 7, line 4. As this amendment does not involve new matter, entry is believed warranted and is earnestly solicited.

Claims 1-3, 5-18, and 20-25 remain pending while claims 1-3, 5, 10, 13, 17-18 and 22-25 are currently subject to examination.

35 U.S.C. §103

Claims 1-3, 5, 10, 13, 17-19 and 22-25 are rejected under 35 U.S.C. §103 as unpatentable over Cochran in view of Previte (previously referenced and discussed). Specifically the Examiner asserts that Cochran teaches a process for decreasing development of allergic asthma, including inter alia: exposing an immature mammal to LPS derived from bacterial endotoxin, with exposure achieved by administering an aerosol spray composition (according to the Examiner "nasal aspiration" is an equivalent), where exposure is achieved "after birth and during the maturing life cycle of the mammal" (according to the Examiner, a single administration at between 2 and 3 weeks age is an equivalent). The Examiner notes that Cochran fails to teach administration of IR-LPS in accordance with all of the instant claims, the recited irradiation level of instant claim 2, or wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive immune effect in

the resulting IR-LPS, or wherein a human ages 1 month to 2 years is exposed, or further wherein exposure is on a daily or weekly basis during growth of a mammal.

Previte is applied for the disclosure of detoxification of LPS derived from E.coli as well as disclosure that such irradiation eliminated lethality while retaining antigenicity (the Examiner asserts that this is equivalent to maintenance of Th1 stimulatory effect) and pyrogenicity.

The Examiner further asserts that the instantly recited functional limitations "operable to the Th 1 arm of the mammal's immune system" in claims 1, 22 and 25 and "while reducing interleukin I(IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin" of claim 25 are inherent properties of Previte's IR-LPS, and cites to case law *In re Schreiber* for the legal proposition that where functional limitations may be critical for establishing novelty, but where the PTO has reason to believe they are inherent in the prior art, it may require the application to prove that the subject matter shown in the prior art does not possess the characteristics relied upon.

To establish a motivation, the Examiner notes disclosure in Cochran that "recent studies raised the intriguing hypothesis that exposure to LPS may interact with the immune system in early life and produce a protective environment against the development of asthma and atopy. Despite the potential importance of this phenomenon in the pathogenesis of childhood asthma, only recently have animal models been used to study the interactions between endotoxin and allergic responses as a function of age" and "patients become symptomatic in their first 5 years of life," concluding that Cochran suggests performing the process for decreasing development of allergic asthma in young children under 5 years of age implicitly.

This rejection is traversed and reconsideration is respectfully requested.

The claims under rejection include three independent claims. Independent claim 1 is directed to a process for decreasing development of allergic asthma. The process comprises exposing a neonatal or immature mammal to irradiation-detoxified lipopolysaccharide (IR-LPS) derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of the mammal's immune system, wherein exposure comprises *at least weekly* administration during maturation of the mammal via application of the IR-LPS to a respiratory environment of the mammal. Independent claim 22 is also directed to a process for decreasing development of allergic asthma in a mammal maturing in an overly sterile environment by restoring normal immune system development, the process comprising exposing a neonatal or immature mammal to irradiation-detoxified lipopolysaccharide derived from extracted *E. coli* bacteria endotoxin and operable to stimulate the Th 1 arm of the mammal's immune system, wherein exposure occurs via administration of the IR-LPS during maturation of the mammal. According to independent claim 25, the process for decreasing development of allergic asthma comprises exposing a neonatal or immature human of up to about 2 years of age to irradiation-detoxified lipopolysaccharide derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of the human's immune system while reducing interleukin 1(IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin, wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irradiation-detoxified lipopolysaccharide at a concentration of 5-15 μg/ml.

Applicants emphatically submit that the Cochran disclosure is no more than basic science without any established utility, without potential for the utility enabled by the present invention, and without a mere suggestion of the impact on development of the adaptive immune system by IR-LPS versus LPS, or with respect to the particular efficacy of IR-LPS over LPS in decreasing development of allergic asthma.

Cochran is directed to a study intended to address "the recent hypothesis that bacterial LPS may interact with the immune system in early life to produce a protective environment." Aside from a statement of the thesis, there is no real support and certainly no disclosure of a relevant method. The Cochran study was "designed to characterize the airway responses to LPS in developing mice," yet Cochran notes the insufficiency of the generated data in supporting the thesis, noting in particular the lack of disruption to the Th-1/Th-2 balance and stating that much remains to be investigated.

The Examiner insists that the steps of Cochran are equivalent in essential terms to the steps of the instantly inventive methods. Applicants submit that the difference between the basic science protocol disclosed by Cochran and the present inventive processes are many, many inventive steps apart in both sophistication, real world utility, and demonstrative evidence of an unpredicted and heretofore unknown differential impact of IR-LPS over LPS. This unrecognized impact forms the basis for many of the unpredicted advantages of the present invention, including the ability to decrease development of allergic asthma by treatment of the environment without impacting allergic sensitivities of others living in proximity to the treated subject.

Cochran anesthetizes 2 week old mice and directly applies a saline solution of LPS intranasally, whereas according to the present inventive processes a mist containing IR-LPS is applied to the environment (typically to a living space) of an immature mammal. Application in accordance with the present methods is at least weekly for some period of time during the maturation life cycle of the mammal. This ensures a nearly continual exposure to the IR-LPS across this time frame. In summary form, substantial differences between the method of Cochran and the instant inventive methods include:

Cochran "Method"	**Presently Claimed Process**
basic science w/o real world application	enabled utility
active = LPS	active = IR-LPS

one time treatment during infancy	continual application across relevant maturation period
applied directly to mammal	applied to living environment of mammal

Further, these express "step" element differences confer substantial and patentable differences in the functioning of the respective methods. Cochran discloses a resulting airway hyperresponsiveness that results in a transient decrease in airway response to a single known allergen, methacholine, with no discernable impact on the Th1/Th2 balance, and further discloses complete cellular and functional resolution of these effects by post treatment day 17. Cochran discloses substantial differences in the cellular and functional responses when compared to the present invention, responses which Applicants submit go to the very underpinnings of the present inventive methods. According to Cochran, the LPS treatment fails to disrupt the Th1/Th2 balance. Yet Cochran discloses that this balance is linked to the development of asthma and may be offset in subjects exposed to a nonmicrobial environment. Hence, in order to confer protection against the development of asthma, Cochran seeks to disrupt this balance, yet fails to disclose the sought after result (Cochran, page 274, first column). Generally, Th-1 represents a cellular response while Th-2 represents a humoral response, the former being more implicated in eliciting adaptations in the immune system and the latter reflecting operation of an existing adaptive response, for example, an allergic response. The balance between these operations is understood in the art as critical components of immune memory and the adaptive immune response in general. Implication of the Th-1 response is necessary to success in decreasing development of asthma while implication of the Th-2 system during this period is sought to be minimized. However, a successfully adapted Th-2 response exists in a subject protected from development of allergic asthma.

Cochran, while noting that the decreased airway responsiveness to Mch in LPS-treated subjects is "apparently" supportive of the protective effect theory, notes its own deficiencies with respect to establishing an actual protective effect or forming the basis of an efficacious treatment method, stating "The protective effect of endotoxin on allergic response has not been invariably demonstrated [by these studies]...[and]...further studies [are] warranted to define these interactions" (page 274, second column, bottom of page).

The secondary reference, Previte, fails to overcome the deficiencies of the primary references or to otherwise suggest the present inventive methods. Further, Applicants submit that Previte stands for exactly the opposite "safety" and "antigenicity" contentions as those put forth by the Examiner and fails to suggest or enable the instant invention. Applicants note that Previte is a 40+ year old reference with results that suggest an untenably high fatality rate among the IR-LPS treated subjects and an undesirable decrease in antigenicity upon irradiation in accordance with the Previte methods.

First, Applicants note that the Examiner's assertion that the IR-LPS of Previte could be safely imported into the methods of Cochran is unsupported and fails to consider the "relative" language/position of Previte. Although Previte reports a decrease in toxicity in bacterially derived LPS in general, lethality is still demonstrably higher than what would be considered acceptable in a treatment or prophylactic protocol. Further, the overall decrease in toxicity, according to Previte, is inconsistent across bacterial species. In particular, for E.coli LPS which Previte discloses as exhibiting the highest loss of toxicity upon irradiation, a 10% retention of toxicity after 20 Mrad is disclosed (see Figure 1, page 1610). Applicants note that 20 Mrad exceeds the top of the range recited in instant claim 2.

Second, the Examiner asserts that the IR-LPS of Previte retained antigenicity and therefore "stimulated the Th-1 arm of an animal's immune system in accordance with the present methods." Applicants submit first that this is an unsubstantiated and erroneous "if-

then" relationship as there is no one-to-one correspondence understood in the art to exist between antigenicity in general, and stimulation of the Th-1 arm of an animals immune system specifically, although there is significant correlation. Regardless, Applicants submit that this statement is an erroneous interpretation of Previte. Applicants note that Previte actually discloses a startling decrease in antigenicity (see page 1611, top of page comparing LPS, 5 Mrad-LPS, and 20 Mrad-LPS, where mean survival times (scope of protection of vaccination) decreased respectively, and where "when six days elapsed between vaccination and challenge, the decrease in antigenicity caused by radiation was more evident." See also, page 1611, second column "The data recorded 21 days after challenge likewise indicated more extensive inactivation of antigenic components with increasing radiation dose"). Applicants note that Previte is more absolute in his conclusory statements, using terms like "complete elimination" to describe impact on toxicity and "slight decrease" to describe antigenicity," but assert that this reflects a relative posture in comparison to previous data cited in Previte, and also is disclosed to reflect results at the most extreme Mrad endpoint of 20 Mrad, outside the scope of the instant invention.

Previte further teaches that the conditions of irradiation, including temperature and opportunity for free radical formation/ presence of water are all factors which may cause significant variance in results (see page 1613, top of first column) so that one IR-LPS is not necessarily equivalent to another on a reference by reference basis. Finally, Previte hypothesizes that the difference in impact on antigenicity over time may be explained because "Radiation may leave specific determinants intact, allowing LPS to elicit the release of 'natural antibodies' and thus increase 'nonspecific resistance'...while more effectively destroying those responsible for 'specific antibody production (measured by protection after challenge at 6 days postvaccination)" and suggests further research to elucidate (see page 1613, bottom of first column). Applicants note that the results of Previte are not directly

applicable nor do they predict results with respect to IR-LPS in general since Previte administers IR-LPS to adult subjects and is not concerned with effects or differences with respect to a developing immune system.

In addition to the fact that the results derived from the IR-LPS of Previte would not suggest the functioning of IR-LPS in accordance with the present invention, Previte fails to teach or suggest any relationship to or enhanced efficacy of LPS with respect to decreasing development of allergic asthma by virtue of the irradiation, as presently discovered, disclosed and exploited by the present inventive methods. Previte administers IR-LPS directly to adult mammals. The present specification teaches that the effect of exposure to LPS and IR-LPS (or any potential allergen) is different in the developing immune system versus the adult immune system and this difference is critical to the instant methods.

Due to the substantial safety issues remaining with even the 20 Mrad IR-LPS of Previte, Applicants submit that a person of ordinary skill in the art would not be guided by the Previte disclosure to import the IR-LPS of Previte into the experimental protocols of Cochran to achieve the instant invention, which is primarily prophylactic in utility. Further, due to the Previte express suggestion that the components of antigenicity relating to adaptation of the immune system for response to future challenges are "destroyed" by irradiation, a person of ordinary skill in the art would be discouraged from the use of IR-LPS specifically to effectuate the long term protective effects and decrease in asthma targeted by the present invention. Finally, assuming arguendo that a person of ordinary skill in the art did import the IR-LPS of Previte into the protocols of the primary references, this still would not overcome the deficiencies noted above, that is, the different time frames for application and the different mode of application, both of which are critical to the efficacy of the present inventive methods.

Applicants submit that the Examiner's assertion that the functional characteristics of IR-LPS recited in the instant claims are inherent to IR-LPS barring specific data demonstrating a difference is actually inapposite to the patentability of the instant methods over these references. As to the merits of the assertion, Applicants note that even Cochran suggests an interplay in effectuated response relating to age of exposure, and Khan notes interplay with the dose of radiation, while the present inventors further recognize the importance the exposure time frame in terms of duration and the exposure via a particular route, all of which impact the response of the immunes system, so that there is no "inherency" with respect to a given active without multiple other controls being instigated.

Without regard to the merits of this assertion, Applicants note that recognition of an inherent characteristic and exploitation of that previously unrecognized characteristic in a method may confer patentability to that method, regardless of inherency. So, for example, if IR-LPS is "operable to stimulate the Th-1 arm" of the immune system without substantially impacting the Th-2 arm, this permits application of IR-LPS to an environment shared by both immature and mature mammalian species, so that the developing immune system of the former may be positively impacted while the developed and perhaps sensitive immune system of the latter would not be negatively impacted. A person of ordinary skill in the art, in the absence of this insight provided by the present disclosure, would not be guided toward such a method, even with awareness of IR-LPS, per se.

Applicants note once again that none of the cited prior art teaches or suggests that irradiated LPS derived from extracted bacterial endotoxin has Th 1 stimulating properties, especially with attenuated IL-1 stimulating properties, and with reduced Th 2 stimulating properties, compared to native LPS (see Declaration, Dr. Sipka, submitted October 2007), a recognition that would be necessary to be guided to realization of the instant inventive methods.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). Cochran fails to teach or suggest a method comprising *more than a single treatment* with non-irradiated LPS applied directly to the subject, whereas the present independent claims require a duration of exposure by, e.g. repeated administration across a maturation period of the subject with application to the subject's living environment. While Cochran posits that certain data "appears" consistent with the original hypothesis that LPS confers a protective effect against allergic asthma, Cochran admits that the actual results fail to yield a disruption in the Th1/Th2 balance, a disruption that Cochran teaches is implicated in restoring a normal Th1/Th2 balance to protect against the development of asthma. The secondary reference, Previte, which teaches single doses of IR-LPS to adult subjects to investigate the relationship between irradiation and retention of lethality and antigenicity, fails to overcome the deficiencies of Cochran, and, in fact, teaches that components of antigenicity relating to long term adaptations of the immune system (such as that which would be necessary to protect against development of asthma) may be destroyed by the levels of radiation needed for sufficient detoxification. There is no motivation in either reference to combine the teachings, since Previte is directed to treatment of adult subjects and teaches retention of an unacceptable degree of toxicity for medical uses, and further teaches against uses of IR-LSP for eliciting an adaptive immune response. Finally, importation of the IR-LPS of Previte into the Cochran protocol still fails to enable the present methods, which require exposure during a maturation period of the developing mammal and exposure by application to the environment of the mammal.

Hence, the rejection of claims 1-3, 5, 10, 13, 17-19 and 22-25 under 35 U.S.C. §103 over Cochran in view of Previte is overcome. Reconsideration is respectfully requested.

Claims 1-3, 5, 10, 13, 17-19 and 22-25 are rejected under 35 U.S.C. §103 as unpatentable over Khan in view of Previte (previously referenced and discussed). Preliminarily, Applicants note investigator overlap between Khan and the primary reference Cochran, addressed above. Khan teaches administration of LPS to immature mice intratracheally and otherwise conducts the same investigatory protocol as Cochran. However, Khan specifically notes that treatment with LPS did not affect allergen-induced airway hyperresponsiveness (AHR), and concludes that "airway exposure to LPS produces transient AHR and inflammation in developing mice and does not appear to influence functional and immune responses induced by subsequent allergen sensitization" (see Poster Board 219). (Applicants further draw attention to the fact that Cochran and Khan are part of the same investigative team and yet publish opposing findings in the same publication year regarding impact on subsequent allergen sensitization.)

Khan, therefore, exhibits the same deficiencies as Cochran (set forth in detail above) with respect to the missing elements defining the inventive methods, and expressly teaches away from the present methods by re-phrasing the more conservative and circumscribed conclusions of Cochran regarding "support" but lack of "invariable" evidence, into a more express teaching that LPS does not appear to influence the very responses sought to be elicited by the instant invention. Previte, as noted above, is directed to studying the efficiency of ionizing radiation in detoxifying the lethal determinant of LPS of various bacterial species and fails to teach or suggest the immunostimulatory properties of irradiated LPS that underpin the instant inventive methods. Not only is there an absence of any express or implied motivation to combine these references, Previte provides secondary evidence of nonobviousness by suggesting that the level of irradiation necessary to effectively detoxify

LPS results in destruction of the components of antigenicity that may be related to eliciting a long term adaptive immune response. Hence, a person of ordinary skill in the art seeking methods to decrease development of allergic asthma would be discouraged from employing the IR-LPS of Previte into the protocols of Cochran or Khan. There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000).

Accordingly, the presently claimed processes defined by claims 1-3, 5, 10, 13, 17-19 and 22-25 are nonobvious over Khan in view of Previte, wherein the rejections under 35 U.S.C. §103 have been overcome.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §103 and places the present application in condition for allowance. Nonetheless, since this application has been subject to protracted prosecution Applicants urge the Examiner to contact their agent below to efficiently address issues which the Examiner believes remain unresolved. Reconsideration and an early allowance are respectfully requested.

Respectfully submitted,

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